REMARKS

I. Status of the claims

Claims 1 and 3 are pending in this application, with claims 2 and 4-17 canceled. Claim 1 has been amended in order to more clearly explain the subject matter of the invention. No claim was amended in order to overcome prior art. Furthermore, the scope of the claims was not narrowed by these amendments. Support for these amendments can be found in originally-filed claim 1 and in the specification at p. 2, line 30 to p. 3, line 5. Accordingly, no new matter has been added by these amendments.

II. Rejections under 35 U.S.C. § 112, first paragraph

The Office rejected claims 1 and 3 under 35 U.S.C. § 112, first paragraph as containing subject matter that was not described in the specification in such a way as to allow one skilled in the art to make and/or use the invention. The Office argues that "[o]ne cannot determine if the test substance inhibits or acts as a ligand of the binding domain, the catalytic domain or both. The written description in the specification as originally filed fails to teach one of skill how to accomplish this." Office Action at p. 2, lines 18-22. Applicant respectfully traverses this rejection.

The specification clearly conveys to the skilled artisan how to determine whether a test substance inhibits or acts as a ligand of the binding domain of a protein. After mixing the test substance with the protein and a marker substrate, these inhibitors or ligands "can be detected by comparing the transformation of the marker substrate in the presence of the test substance with the corresponding transformation occurring in appropriate control mixtures." Specification at p. 12, lines 8-10. One such control

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mixture (labeled control A in claim 1) contains the protein and the substrate marker but no substrate or test substance (*e.g.*, Example 1 in Table 1). "The transformation of the marker substrate in this control mixture indicate[s] the maximum conversion possible for the marker substrate because there [is] no inhibition of the catalytic domain." Example 1 at p. 12, lines 12-15.

Another control mixture (Control B in claim 1) contains the protein, the substrate marker, and the substrate but again, no test substance (*e.g.*, Example 2 in Table 1). The conversion of the marker substrate in this mixture is lower than that in control mixture A. This is because "[t]ransformation of the marker substrate in this second control mixture reflect[s] competitive inhibition of the catalytic domain by both the substrate and the marker substrate." Example 2 at p. 12, lines 19-21.

"If conversion of the marker substrate in the presence of a test substance is between the values obtained with these two control mixtures [Controls A and B], an inhibitor or ligand of the protein has been found." Example 2 at p. 12, lines 23-25.

The claimed methods are graphically explained in the following diagram.

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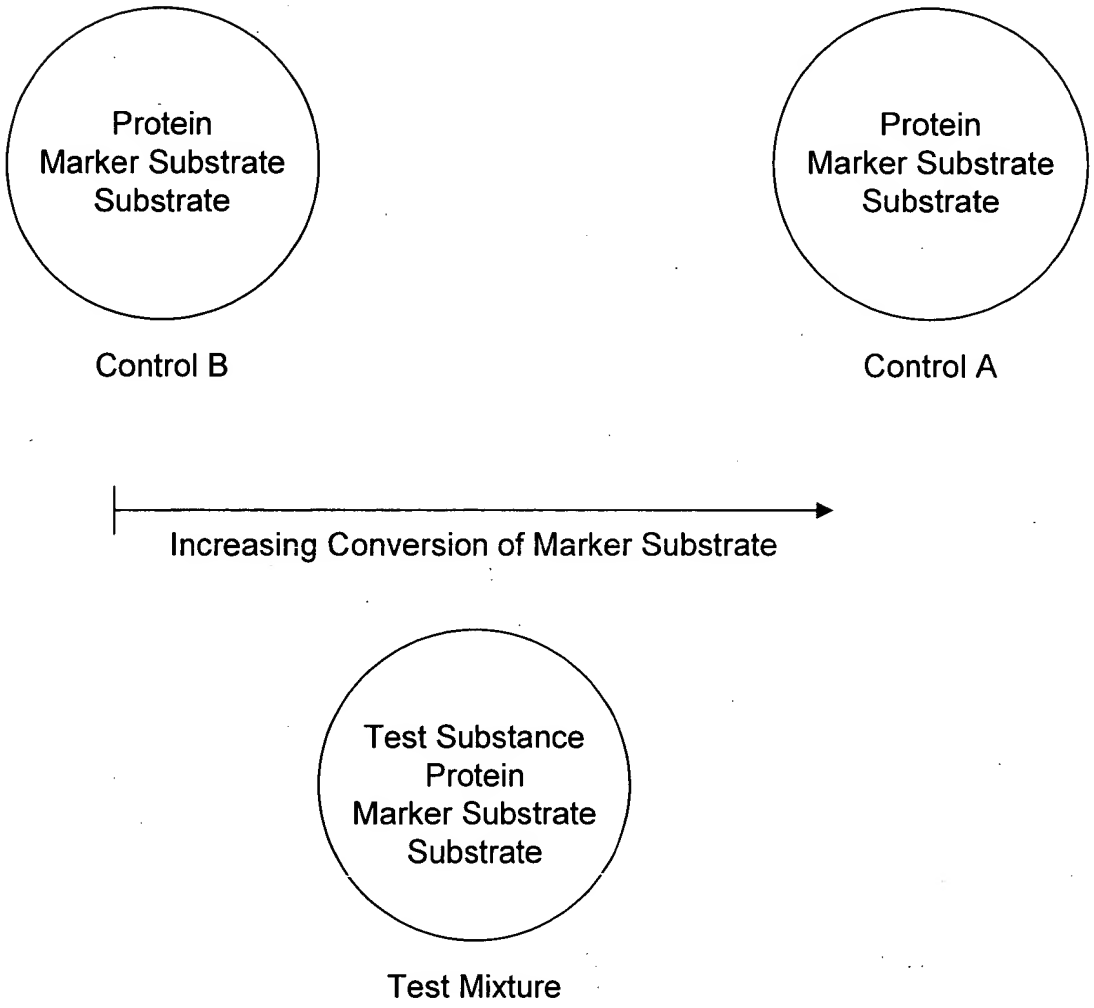

Conversion of the Marker Substrate in the Test Mixture falls between the conversion observed for Control mixtures A and B.

The method just described, coupled with the teachings of Examples 3, 5, and 6, can be applied to the determination of whether a test substance is an inhibitor or a ligand of any protein that has at least one binding domain and at least one catalytic domain.

In light of the foregoing remarks, the specification as originally filed clearly teaches the skilled artisan how to determine whether a test substance inhibits or acts as

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a ligand of the binding domain of a protein. Accordingly, Applicant respectfully requests that this rejection be withdrawn.

The Office also argues that the specification does not disclose "[h]ow to find [a marker substrate and a] substrate for any protein to effectively determine any test compound." Office Action at p. 2, line 23 to p. 3, line 6. Applicant respectfully disagrees.

Applicant respectfully reminds the Office that enablement needs to be analyzed, *inter alia*, in light of the state of the prior art. M.P.E.P. § 2164.01(a). There is a large number of enzymes and their substrates known in the prior art. For example, the International Union of Biochemistry and Molecular Biology has compiled a list of known enzymes, including their function, and their most common substrates in *Enzyme Nomenclature*, 6th Ed. Academic Press, San Diego, CA (1992); ISBN 0-12-227164-5 (hardback), 0-12-227165-3 (paperback). In the 1992 publication, the list disclosed 3,196 enzymes. This compilation has been updated periodically and, in the last printed supplement, the number of enzymes disclosed was over 5,000. Supplement 5, Eur. J. Biochem. 264:610-650 (1999). Web versions of the printed supplements 1-5 and the web-only supplements 6-8 are available at http://www.chem.qmul.ac.uk/iubmb/enzyme/archive.html. Therefore, it is clear that numerous protein-substrate pairs are known in the art.

Similarly, various methods are well known to prepare marker substrates once a substrate for a particular protein is known. In the most common method, a fluorogenic marker is attached covalently to a fragment of the substrate that binds to the catalytic site of the protein. See, e.g., U.S. Patent No. 5, 770, 691; Stack, M. Sharon, et al.,

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Journal of Biological Chemistry 264(8):4277-4281 (1989); Nagase, Hideaki et al., Journal of Biological Chemistry, 269(33):20952-20957 (1994); Niedzwiecki, Lisa et al., Biochemistry, 31:12618-12623 (1992); Knight, C. Graham et al., Federation of European Biochemical Societies Letters, 296(3):263-266 (1992); Bickett, D. Mark et al., Analytical Biochemistry, 212:58-64 (1993). All of these references are already of record in this application. Therefore, selecting an appropriate substrate and a substrate marker for a protein would not involve undue experimentation. In this respect, the Office is reminded that a "considerable amount of experimentation is permissible . . . if the specification provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed." M.P.E.P. § 2164.06.

The Office further argues that the "[q]uantity of experimentation necessary would be undue because of the large proportion of inoperative compounds claimed." Office Action at p. 3, point 1.

Applicant respectfully reminds the Office that the instant claims are drawn to methods to determine whether a test substance is an inhibitor or a ligand of a protein. The instant claims do not claim compounds. If is furthermore unclear what "compounds" the Office is referring to. Applicant reserves the right to address any arguments regarding the enablement of composition claims when and if necessary in future divisional applications. As mentioned previously, the specification clearly conveys to the skilled artisan how to use the methods of the instant invention in general for any given protein that contains at least one catalytic domain and at least one binding domain. See pages 4-6, supra.

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The Office further argues that the "[a]mount of direction or guidance presented is insufficient to predict which substances encompassed by the claims would work." Office Action at p. 3, point 2.

It is unclear what "substances" the Office is referring to. As mentioned previously, the instant claims are drawn to methods, not compositions. Furthermore, there is no element of uncertainty in the instant claims that would require that the specification "predict" which substance would be an inhibitor or ligand of the protein of interest. The claimed method will simply determine whether the test substance is or is not an inhibitor or ligand of a binding domain of the protein of interest.

In light of the foregoing remarks, Applicant submits that the methods of the invention are clearly enabled in their full scope. Accordingly, Applicant respectfully requests that this rejection be withdrawn.

III. Rejections under 35 U.S.C. § 112, second paragraph

The Office rejected claims 1 and 3 under 35 U.S.C. § 112, second paragraph, as being allegedly indefinite for failing to point out and distinctly claim the subject matter of the invention.

The Office argues that claim 1 as presently stated will not perform the method of the preamble apparently because some characteristics of "protein", "substrate", and "substrate marker" are not defined within claim 1. Applicant respectfully traverses this rejection.

Applicant respectfully reminds the Office that definiteness of claim language must be analyzed, *inter alia*, in light of the specification. M.P.E.P. § 2173.02. Because

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suitable definitions of "protein", "substrate", and "substrate marker" are present in the specification (e.g., on page 2, lines 16-23), Applicant does not need to define these terms again in the claims. However, with the sole purpose of expediting prosecution, claim 1 has been amended addressing the Office's concerns. Accordingly, this rejection is now moot and Applicant respectfully requests that the rejection be withdrawn.

IV. CONCLUSION

In view of the foregoing amendments and remarks, Applicant respectfully requests the reconsideration and reexamination of this application and the timely allowance of the pending claims.

Please grant any extensions of time required to enter this response and charge any additional required fees to our deposit account 06-0916.

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